The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PCT/EP03/7615

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Signed Stephen Hordley

Dated 26 June 2003

Pate[illegible] Form 1/77

[illegible] Act 1977
16)

THE PATENT OFFICE
B
12 JUL 2002
LONDON

The Patent Office

PCT/EP03/07615

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

0216233.7

12 JUL 2002

P01/7700 0.00-0216233.7

1.	Your Reference	PF4879
2.	Patent application number *(The Patent office will fill in this part)*	
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	GLAXO GROUP LIMITED ~~980 GREAT WEST ROAD BRENTFORD MIDDLESEX TW8 9GS~~ GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 0NN
	Patents ADP number *(if you know it)*	04887006
	If the applicant is a corporate body, give the country/state of its corporation	
4	Title of the invention	COMPOUNDS
5	Name of your agent *(if you know one)*	JANETTE Y ROWDEN
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXOSMITHKLINE 980 GREAT WEST ROAD BRENTFORD MIDDLESEX TW8 9GS
	Patents ADP number *(if you know it)*	08687001

AD 20/77 10.10.02

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	41
Claim(s)	3
Abstract	3
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature JANETTE Y ROWDEN J. Rowden
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

LYNNE SAWKINS
020 8047 4461

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication of communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the patent Act 1977 stops you from applying for a patent abroad without first getting written permission form the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been received

a) *Notes*

If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form*

If you have answered "Yes" Patents Form 7/77 will need to be filed.

d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

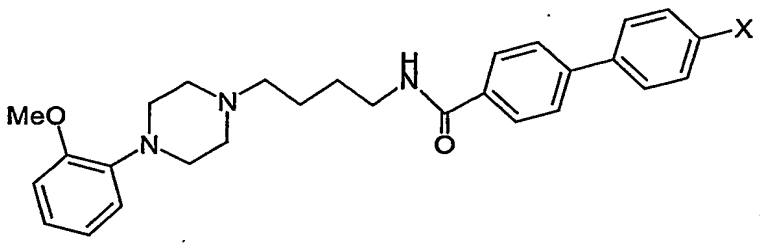
Therapeutic Aryl Piperidine Derivatives

This invention relates to novel compounds which up-regulate LDL receptor (LDL-r) expression and to processes for their preparation, pharmaceutical compositions containing them and their medical use. More particularly, this invention relates to novel aromatic piperidines and their use in therapy.

Epidemiological studies have clearly demonstrated the correlation between reduction in plasmatic LDL cholesterol and the benefit on cardiovascular events including mortality. LDL cholesterol is eliminated from plasma by specific binding to LDL-r expressed by the liver. Regulation of LDL-r expression occurs in the liver and is mainly dependent on intracellular cholesterol concentration. Increasing free cholesterol concentration leads to a reduced LDL-r expression through a mechanism involving transcriptional factors. Counteracting with this process is expected to up-regulate LDL-r expression in the liver and to increase the clearance of LDL cholesterol.

International Patent Application Number PCT.EP00.06668 concerns the novel use of the SREBP-cleavage activating protein (SCAP) in a screening method, and two compounds are disclosed, namely 4-(4-chloro-benzoylamino)-N-{4-[4-(2-ethoxy-4-ethyl-phenyl)-piperidin-1-yl]-butyl}-benzamide and 4-(4-Benzoyl)-N-{4-[4-(4-isopropyl-2-methoxy-phenyl)-piperidin-1-yl]-butyl}-benzamide hydrochloride, which do not form part of the present invention.

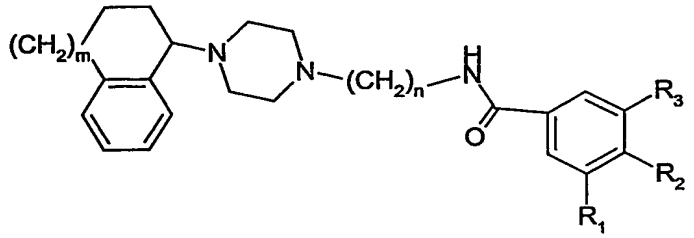
Another publication, Bioorganic and Medicinal Chemistry Letters Vol. 5, 3, 219-222, 1995 discloses compounds having the general formula (A)



A

where X may be COMe, SO_2Me and NH_2, as having high affinity for the dopamine D_3 receptor and postulates their use in CNS disorders, particularly psychiatric illness. The compound of formula A where X is COMe is also disclosed in J.Pharmacol. Exp. Ther. 287; 1 1998 187-197 and Bioorganic and Medicinal Chemistry Letters Vol. 7, 15, 1995-1998, 1997, again as being useful in treating CNS disorders. It will be noted that the examples of the present invention differ from those of formula (A) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

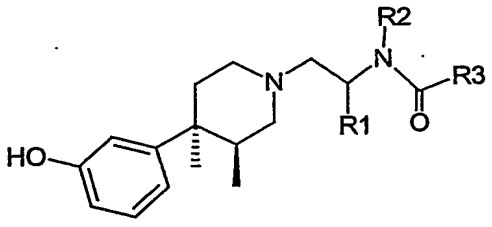
Journal Of Medicinal Chemistry, Vol. 40, 6, 952-960, 1997 discloses compounds of formula (B)



B

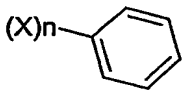
where m=0,1 or 2; n=2 or 3; R_1 and R_3= H or OMe and R^2 may be Ph, as selective 5-HT_{1A} receptor ligands having CNS activity. It will be noted that the examples of the present invention differ from those of formula (B) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO99/45925 discloses compounds of formula (C)



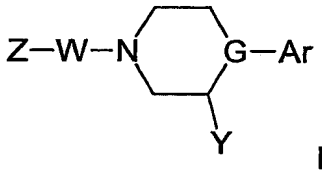
C

where R1 may be hydrogen, R2 may be hydrogen and R3 may be a group



where X may be an aryl group and n may be 1. Specifically disclosed are compounds where the group COR3 is formed from 2- and 4- biphenyl carboxylic acid and R1 and R2 are methyl or hydrogen respectively. The utility of the compounds is as opioid receptor binding agents which may be useful as analgesics. The substitution on the 3- and 4- positions of the piperidine ring leave the compounds of this publication outside the scope of the present invention. Furthermore, the utility disclosed is different.

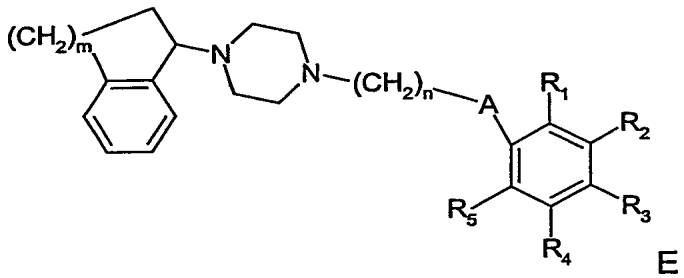
International Patent Application Publication Number WO98/37893 discloses compounds of formula (D)



D

where Ar may represent an optionally substituted phenyl or naphthyl, G may be N or CH_2 (*sic*), W may be an optionally substituted alkylene, Y may be hydrogen and Z may represent a group R_4CONR_5, where R_4 may be an optionally substituted phenyl and R_5 may be hydrogen. These compounds are described as being D2 receptor antagonists useful in the treatment of CNS disorders such as Parkinson's Disease. None of the compounds specifically disclosed fall within the scope of the present invention and the disclosed utlity is different.

International Patent Application Publication Number WO9402473 discloses compounds of formula (E)



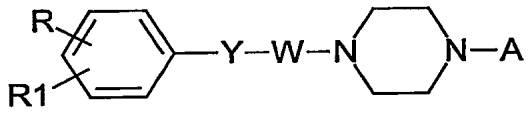
E

where A may be NHCO or CONH; R_1-R_5 may be hydrogen or a benzene ring, m may be 1-3 and n may be 1-3. Specifically disclosed are the following compounds:

No.	A	n	m	R_1	R_2	R_3	R_4	R_5
5	NHCO	2	1	H	H	Ph	H	H
12	NHCO	2	2	H	H	Ph	H	H
19	NHCO	2	3	H	H	Ph	H	H

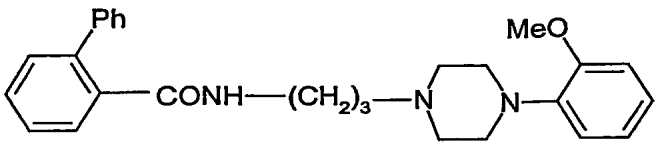
The compounds are described as 5HT-1A agonists having CNS activity and may be used as anti-depressants, anti-hypertensive, analgesics etc. It will be noted that the examples of the present invention differ from those of formula (E) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO99/45925 discloses compounds of formula (F)



F

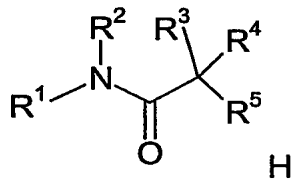
where A may represent a substituted phenyl group, W represents a linear or branched alkylene group having from 2 to 6 carbon atoms; Y may represent a group NHCO or CONH; and R may be a substituted phenyl group. Particularly disclosed is the compound G



(G)

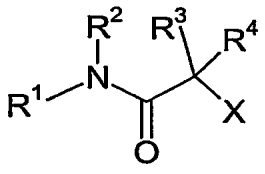
These compounds are described as being α1A-adrenergic receptors useful in the treatment of contractions of the prostate, urethra and lower urinary tract, without affecting blood pressure. It will be noted that the examples of the present invention differ from those of formula (G) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO98/35957 describes compounds of formula (H)



H

wherein R1-R5 are each individually selected from the group of substituents including hydrogen, halogen, hydroxyl, thiol, lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkylalkenyl, alkylalkynyl, alkoxy, alkylthio, acyl, aryloxy, amino, amido, carboxyl, aryl, substituted aryl, heterocycle, heteroaryl, substituted heterocycle, heteroalkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, alkylcycloheteroalkyl, nitro and cyano. Specifically disclosed compounds are those formed by the N-alkylation of a a substituted piperidine or piperazine with a group (J)

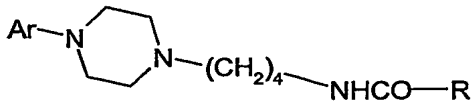


(J)

where X is a leaving group. None of the compounds specifically disclosed fall within the scope of the present invention and the invention is in no way suggested by the disclosure. The compounds are said to be of use as NPY Y5 receptor antagonists in the treatment of obesity, bulemia and related disorders

and NPY Y5 receptor inhibition related disorders such as memory disorders, epilepsy, dyslipidemia and depression. US Patent no. 6,048,900, published after the priority date of the present invention discloses the same information.

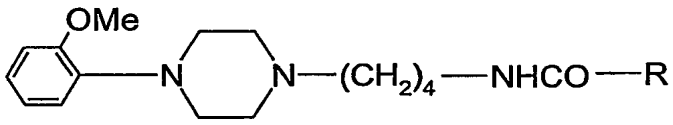
Journal Of Medicinal Chemistry, Vol. 31, 1968-1971, 1988 discloses certain aryl piperazines compounds, which fall outside the present invention, as 5HT-1a Serotonin Ligands as potential CNS agents. Specifically disclosed are compounds of formula (K)



(K)

where Ar=Ph and R = Ph, Ar= 2-OMePh and R =Ph and Ar=2-pyrimidyl and R=Ph.

Journal Of Medicinal Chemistry, Vol. 34, 2633-2638, 1991 discloses aryl piperazines having reduced α1 adrenergic affinity. Specifically disclosed is the compound (L)

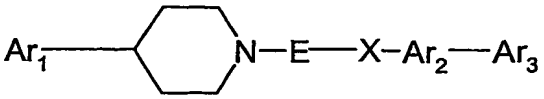


(L)

where R is 4-(BnO)-phenyl, which falls outside the scope of the present invention.

The present invention provides aryl piperidine derivatives which are particularly useful in treating cardiovascular disorders associated with elevated levels of circulating LDL-cholesterol.

Thus, the present invention provides, as a first aspect, a compound of formula (I)



(I)

wherein

Ar_1 represents

(i) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl , or

(ii) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that at least one ring is aromatic,

where Ar_1 bears at least one group independently represented by R^1 and 0-3 groups independently represented by R^3;

R^1 is $O(CH_2)_nOR^2$;

R^2 is H or $(CH_2)_mCH_3$;

n is 1-4;

m is 0-4;

R^3 is selected from halogen, -O-(C_{0-4} alkylene)-R^4 or –(C_{0-4}alkylene)-R^4, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms ;

R^4 represents

(i) hydrogen, C_{1-4} perfluoroalkyl, C_{1-4}perfluoroalkoxy,

(ii) phenyl, phenyl fused by a C_{3-8}cycloalkyl , naphthyl or a 5- or 6-membered heteroaromatic group, optionally substituted by one or two groups

independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino,

(iii) C_{3-8}cycloalkyl or a monocyclic heterocyclyl radical containing a total of 3-7 ring atoms, wherein said radical contains a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein said radical may be independently saturated, partially unsaturated, or aromatic, and where the C_{3-8}cycloalkyl or a monocyclic heterocyclyl may bear one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino, or

(iv) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino;

Ar_2 represents phenyl or a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, where each group is optionally substituted by one or two groups independently selected from the group consisting of: C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, C_{1-6} acyl, C_{1-6} acyloxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino groups;

Ar_3 represents

(i) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl,

(ii) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

where Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkoxy, C_{1-4} acylamino or an electron withdrawing group selected from the list consisting of: nitrile, nitro, C_{1-4}, C_{1-4} perfluoroalkyl, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylaminosulfonyl and di-C_{1-4} alkylaminosulfonyl, C_{1-4} alkylsulfonyl and C_{1-4}alkylsulfoxy;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

or a physiologically acceptable prodrug, salt or solvate thereof.

As used herein the term "physiologically acceptable" means a compound which is suitable for pharmaceutical use.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable inorganic acids for example, hydrochlorides, hydrobromides or sulphates, or with pharmaceutically acceptable organic acids for example mesylates, lactates and acetates. More suitably, a physiologically acceptable salt of the compounds of general formula (I) is a mesylate salt.

The solvates may, for example, be hydrates.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol, sulfhydryl and amine functional groups of the compounds of structure (I). Further, in the case of a carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like.

References hereinafter to a compound according to the invention include compounds of formula (I) and their physiologically acceptable prodrugs, salts and solvates.

Referring to the general formula (I), alkyl, alkylene and alkoxy include both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl and ethyl groups, examples of alkylene groups include methylene and ethylene groups, whilst examples of alkoxy groups include methoxy and ethoxy groups.

Referring to the general formula (I), alkenyl includes both straight and branched chain saturated hydrocarbon groups containing one double bond. Examples of alkenyl groups include ethenyl or n-propenyl groups.

Referring to the general formula (I), acyl refers to aliphatic or cyclic hydrocarbons attached to a carbonyl group through which the substituent bonds, such as acetyl.

Referring to the general formula (I), phenyl fused by a C_{3-8}cycloalkyl includes bicyclic rings such as 1,2,3,4-tetrahydronaphthyl, which, for the avoidance of doubt, is linked to the rest of the molecule through the aromatic ring.

Referring to general formula (I), a halogen atom includes fluorine, chlorine, bromine or iodine.

Referring to the general formula (I), C_{1-3}perfluoroalkyl and C_{1-3}perfluoroalkoxy includes compounds which the hydrogens have been partially or fully replaced by fluorines, such as trifluoromethyl and trifluoromethoxy or trifluoroethyl.

Referring to the general formula (I), a 5-6 membered heteroaromatic group includes a single aromatic ring system containing at least one ring heteroatom independently selected from O, N and S. Suitable examples include pyridyl and thiazolyl.

Referring to the general formula (I), a C_{3-8} cycloalkyl group means any single carbocyclic ring system, wherein said ring is fully or partially saturated. Suitable examples include cyclopropyl and cyclohexyl groups.

Referring to the general formula (I), a 3-7 membered heterocycloalkyl group means any single ring system containing at least one ring heteroatom independently selected from O, N and S, wherein said ring is fully or partially saturated.

Preferably, Ar_1 represents phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indole, benzofuran or benzthiophene. More preferably, Ar_1 represents phenyl, 1,2,3,4-tetrahydronaphthyl or indole.

Where Ar_1 is 1,2,3,4-tetrahydronaphthyl, the link to the piperidine ring is preferably through the 2- position of the 1,2,3,4-tetrahydronaphthyl moiety and mono-substitution by R^1 is in the corresponding 1- position.

Where Ar_1 is indole, the link to the piperidine ring is preferably through the 3-position of the indole moiety and mono-substitution by R^1 is in the corresponding 1- position.

Where Ar_1 is naphthyl, the link to the piperidine ring is preferably through the 1- or 2- position of the naphthyl moiety and mono-substitution by R^1 is in either the corresponding 2- or 1- positions respectively.

R^1 is preferably $O(CH_2)_2OCH_2CH_3$ or $O(CH_2)_2OH$.

E is preferably an n-butylene group.

X is preferably a -N(H or C_{1-4} alkyl)CO- group, more preferably an -N(H)CO- group.

Preferably, Ar_2 represents phenyl or a 5-6-membered heteroaromatic group. More preferably Ar_2 represents phenyl, thiazolyl or oxadiazole.

Ar_3 is preferably a phenyl or pyridyl group, suitably 2-pyridyl. Ar_3 is preferably substituted by halogen, e.g. chloro or C_{1-4}perfluoroalkyl, e.g. trifluoromethyl, nitrile, C_{1-4}acyl, e.g. acetyl, or C_{1-4}alkylsulfonyl, e.g. methylsulfonyl.

When Ar_3 is phenyl, para- substitution is preferred.

Particularly preferred compounds of the invention include those in which each variable in Formula (I) is selected from the preferred groups for each variable. Even more preferable compounds of the invention include those where each variable in Formula (I) is selected from the more preferred or most preferred groups for each variable.

The compounds of the invention are inducers of LDL-r expression and are thus of use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

The ability of the compounds of the invention to induce LDL-r expression by human hepatocytes in vitro is determined using a human hepatocarcinoma cell line, Hep G2, as a model system. A reporter gene assay using the LDL-r promoter in front of the reporter gene Luciferase is used as a primary screen.

The in vivo profile of the compounds is evaluated by oral administration of the compounds of the invention to fat-fed hamsters. Measurements of VLDL/LDL cholesterol and triglycerides upon treatment allow the activity to be determined.

The compounds of the invention are potent and specific inducers of LDL-r expression, which furthermore exhibit good oral bioavailability and duration of action.

Compounds of the invention are of use in the treatment of diseases in which lipid imbalance is important, e.g. atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), coronary heart diseases and obesity.
Compounds of the invention are also useful in lowering serum lipid levels, cholesterol and/or triglycerides, and are of use in the treatment of hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia.

The invention therefore provides a compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol, comprising administration of an effective amount of a compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a physiologically acceptable prodrug, salt or solvate thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, transdermal, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with

pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

For transdermal administration the compounds according to the invention may be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilising, dispersing, suspending, and/or colouring agents.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively,

the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

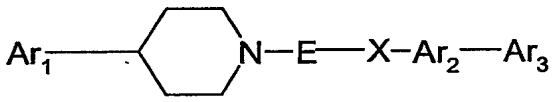
The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

The compositions may contain from 0.1% upwards, e.g. 0.1 - 99% of the active material, depending on the method of administration. A proposed dose of the compounds of the invention is 0.25mg/kg to about 125mg/kg bodyweight per day e.g. 20mg/kg to 100mg/kg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

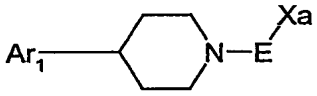
The compounds of formula (I) may, if desired, be administered with one or more therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the compounds of formula (I) may be administered in combination with an HMG CoA reductase inhibitor, an agent for inhibition of bile acid transport or fibrates.

A compound of formula (I), or a physiologically acceptable prodrug, salt, solvate or derivative thereof, may be prepared by the general methods outlined hereafter. In the following description, the groups Ar_1, Ar_2, Ar_3, R^1, R^2, R^3, R^4, E and X are as previously defined for compounds of formula (I), unless specified otherwise.

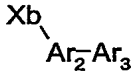


(I)

According to a first general process (A), a compound of formula (I) may be prepared by reaction of a compound of formula (II) with a compound of formula (III)



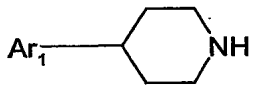
(II)



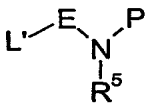
(III)

where Xa and Xb are suitable reactants to form a group X. For example, where X is N(H or C_{1-4} alkyl)CO, Xa is NH_2 or NH(C_{1-4} alkyl) and Xb is COL where L is OH or a suitable leaving group, such as halide. Such a reaction may be effected under standard amide bond-forming conditions, including those described herein.

A compound of formula (II) where Xa is NH_2 or NH(C_{1-4} alkyl), may be prepared by reaction of a compound of formula (IV) with a compound of formula (V)



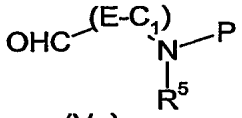
(IV)



(V)

where R^5 represents H or C_{1-4}alkyl, L' is a suitable leaving group, such as halide, and P is any suitable N-protecting group, under standard alkylation conditions, including those described herein, followed by removal of the protecting group under standard conditions.

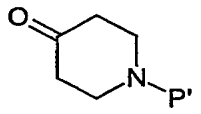
A compound of formula (II) where Xa is NH_2 or NH(C_{1-4} alkyl), may further be prepared by reaction of a compound of formula (IV) with a compound of formula (Va)



(Va)

where R^5 represents H or C_{1-4}alkyl, where E-C_1 ('E minus C_1') means that the chain length of group E is one carbon less than that in the resulting compound (II), and P is any suitable N-protecting group, under standard reductive amination conditions, including those described herein, followed by removal of the protecting group under standard conditions.

A compound of formula (IV) may be prepared by reaction of a compound Ar_1-sal, where sal represents the lithium or magnesium ion of Ar_1, with a compound of formula (VI)

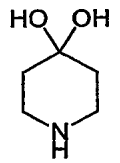


(VI)

where P' represents a suitable N-protecting group, such as acetyl, benzyl or benzyl-4-oxo-1 carboxylate, followed by the steps of dehydration, reduction of the resulting double bond, and finally, removal of the protecting group P' using standard conditions. Such chemistry has been described, for example, in European Patent Application no. 0630887.

Alternatively, a compound of formula (IV) where Ar_1 is substituted by an activated ortho or para activating group for the reaction centre, Act, e.g. methoxy or hydroxy, may be prepared by reaction of a compound of formula Ar_1-Act, with a compound of formula (VI) under suitable reaction conditions such as e.g. trifluoroborane or acetic acid and aqueous hydrochloric acid, to form a tetrahydropyridyl ring, followed by reduction, e.g. under hydrogenation conditions, of the resulting double bond and finally deprotection of the N-protecting group, P' under standard conditions.

Alternatively, a compound of formula (IV) where where Ar_1 is substituted by an activated ortho or para activating group for the reaction centre, Act, e.g. methoxy or hydroxy, may be prepared by reaction of a compound of formula Ar_1-Act, with a compound of formula (VII)

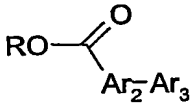


(VII)

under suitable reaction conditions such as e.g. acetic acid and aqueous hydrochloric acid to form a tetrahydropyridyl ring, followed by suitable N-

protection, then reduction, e.g. under hydrogenation conditions, of the resulting double bond and finally deprotection of the N-protecting group.

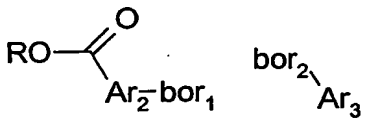
A compound of formula (III) may be prepared by standard methods including, where Xb is CO_2H, deprotection of a compound of formula (X)



(X)

where R is a suitable carboxylic acid protecting group, such as methyl and ethyl.

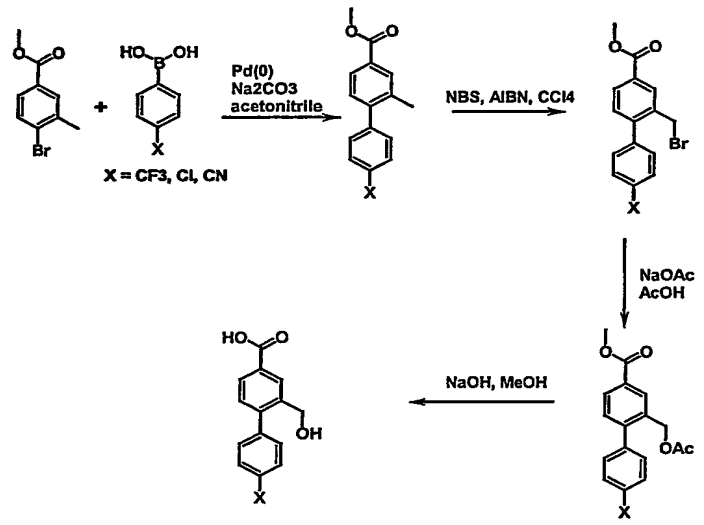
A compound of formula (X) where R is H or a suitable protecting group, may be prepared by reaction of a compound of formula (XI), with a compound of formula (XII)



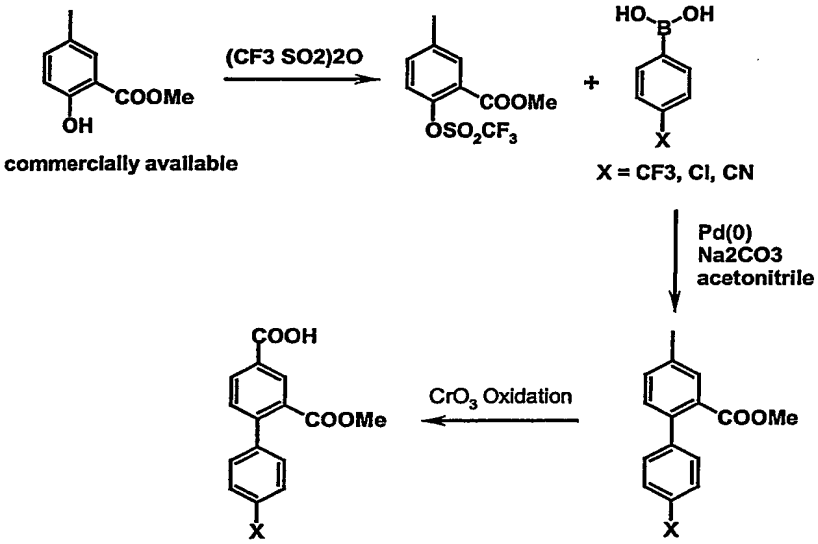
(XI) (XII)

where bor_1 represents a boronic acid group or a halide, e.g. bromide or iodide, and bor_2 represents a suitable boronic acid group or a halide, e.g. bromide or iodide for coupling, under conditions suitable for boronic acid coupling, e.g. using palladium (0) and sodium carbonate.

Schemes 1 and 2 below illustrate examples of the preparation of compounds of formula (X) wherein Ar_2 is phenyl.

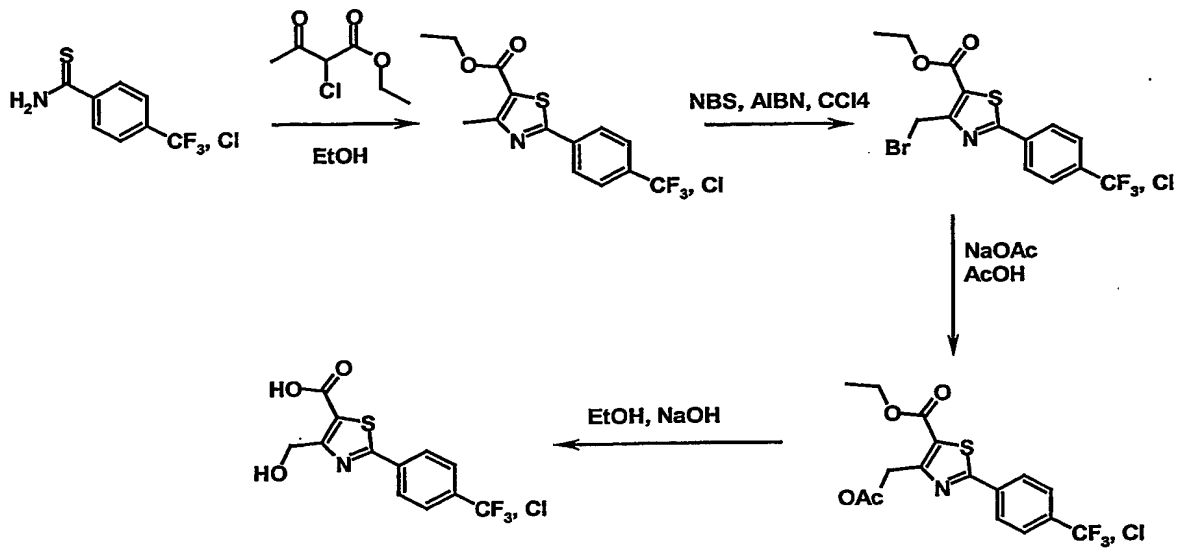


Scheme 1

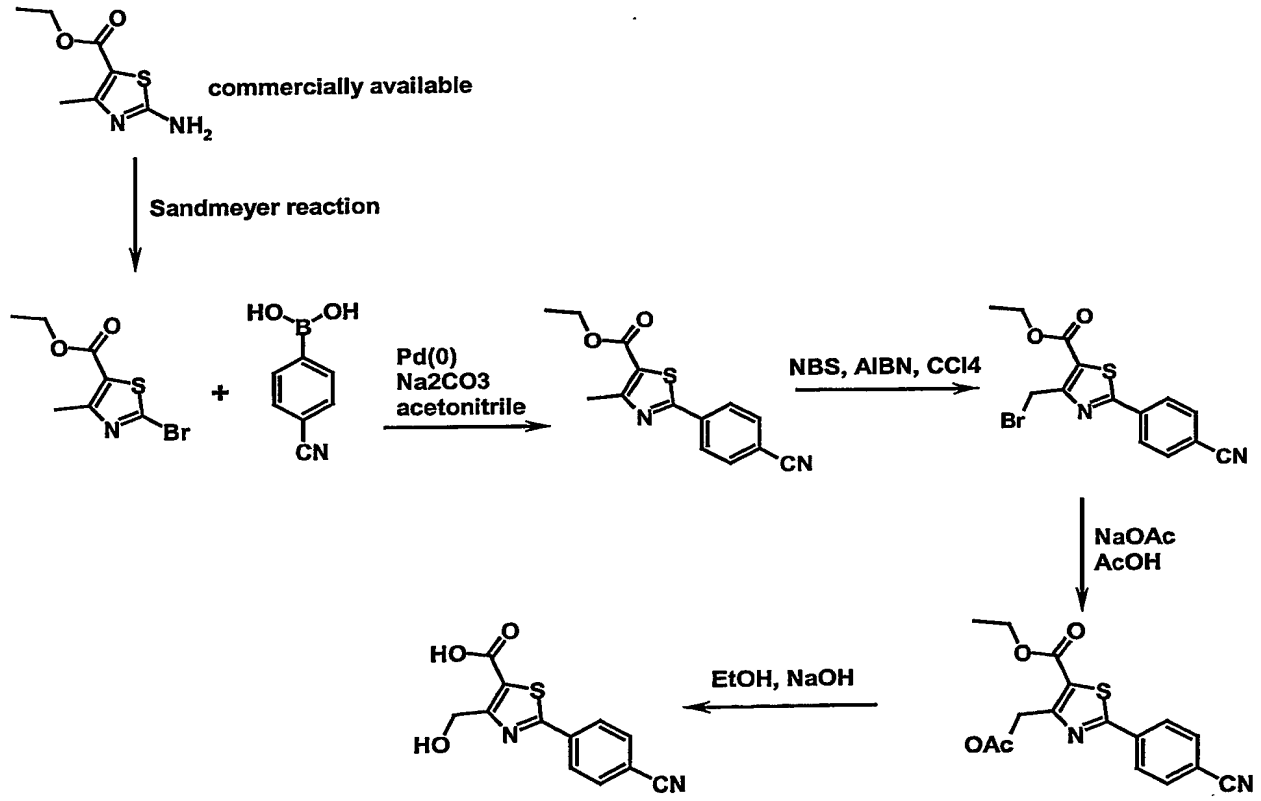


Scheme 2

Schemes 3 and 4 show examples of the preparation of compounds of formula (X) when Ar_2 is a 5-6-membered heteroacromatic group.



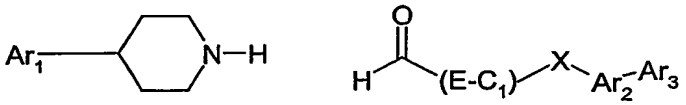
Scheme 3



Scheme 4

It will be apparent to a person skilled in the art that further compounds of formula (X) may be synthesised in an analagous fashion to that illustrated in Schemes 1-4.

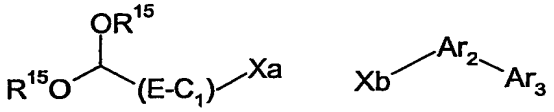
According to a second general process (B), a compound of formula (I) may be prepared by reaction of a compound of formula (IV) with a compound of formula (XIII)



(IV) (XIII)

where E-C_1 ('E minus C_1') means that the chain length of group E is one carbon less than that in the resulting compound (I), under standard reductive amination conditions, e.g. sodium triacetoxyborohydride and acetic acid in a suitable solvent, such as dichloromethane.

A compound of formula (XIII) may be prepared by reaction of a compound of formula (XIV) with a compound of formula (XV)



(XIV) (XV)

where R^{15} is a suitable alkyl protecting group for oxygen, such as methyl, and Xa and Xb are suitable reactants to form a group X, as defined hereinbefore, followed by removal of the protecting group, under acidic conditions.

According to a third general process (C), a compound of formula (I) may be prepared by reaction of a different compound of formula (I), by well known methods. For example a compound of formula (I) where Ar_1 is substituted by C_{1-4} alkoxy may be prepared from the corresponding compound of formula (I) where the substituent is hydroxy by standard O-alkylation methods.

Compounds of formula (V), (VI), (VII), (VIII), (IX), (XI), (XIV) and (XV), are known or may be prepared by standard methods, e.g. as substantially described herein.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed. J. F. W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene and P M G Wuts (John Wiley and Sons 1991).

Conventional amino protecting groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl.

Conventional carboxylic acid protecting groups include methyl and ethyl groups.

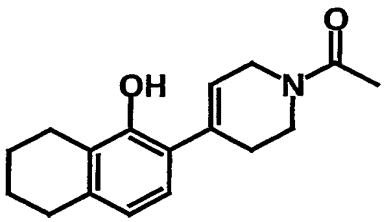
The invention is further described with reference to the following non-limiting examples.

Abbreviations :

$Pd(PPh_3)_4$- Tetrakis-(triphenylphosphine)-palladium(0), THF- Tetrahydrofuran, BF_3-Et_2O- Boron trifluoride diethyl etherate, DCM- Dichloromethane, TEA- triethylamine, CH_3CN- Acetonitrile, EtOH- Ethanol, EtOAc- Ethyl acetate, iPr_2O- Di-isopropyl ether, iPrOH- Isopropanol, Pd/C- Palladium on carbon, Et_2O- diethyl ether, Chex- cyclohexane, MeOH- Methanol, DMF- Dimethyl formamide, EDCI- 1-(3-dimethylaminopropyl)-, ethylcarbodiimide hydrochloride, HOBt- 1-Hydroxybenzotriazole, rt- Room temperature, AcOH- Acetic acid, NaOH- Sodium hydroxide, KOH- potassium hydroxide, HCl- Hydrochloric acid, AcOH- Acetic acid, NaH- Sodium hydride, Na_2SO_4- Sodium sulfate, CCl_4- Carbon tetrachloride, AIBN- 2,2'-Azobis(2-methylpropionitrile), K_2CO_3- Potassium carbonate, Na_2CO_3- Sodium carbonate, NaCl- Sodium chloride,TMAD- N,N,N',N'-tetramethylazodicarboxamide, $POCl_3$- Phosphorus oxychloride, DME-Dimethyl ether, Cs_2CO_3- Cesium carbonate, CrO_3- Chromium(VI) oxide, BBr_3- Boron tribromide.

Intermediate 1

1-[4-(1-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-3,6-dihydro-2H-pyridin-1-yl]-ethanone

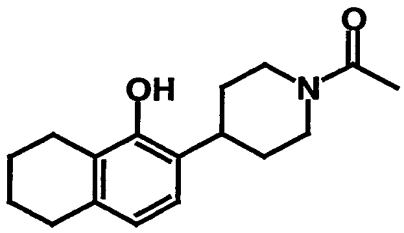


To a solution of 5,6,7,8-tetrahydro-naphthalen-1-ol (20.0 g, 0.135 mol) and 1-acetyl-4-piperidone (22.84 g, 1.2 eq.) in THF (400 mL), was added dropwise BF_3-Et_2O (68 mL, 4.0 eq). The mixture was stirred at 100°C for 2 hours, and 14 hours at room temperature. The mixture was treated with a 1N HCl solution (400 mL). The resulting solution was extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give an oil which was recrystallized in acetonitrile to give the title compound (24.2 g, 89 mmol) as a white crystals in a 66% yield.

GC/MS: M^+ $C_{17}H_{20}NO_2$ 271

Intermediate 2

1-[4-(1-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-ethanone

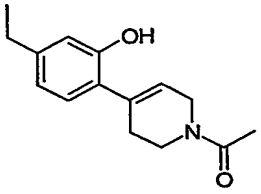


To a solution of intermediate 1 (9.4 g, 34.7 mmol) in EtOH (300 mL) was added Pd/C,10% (0.9 g) and the reaction was stirred under an atmospheric pressure of hydrogen at 25°C for 24 hours. The mixture was filtered through a bed of celite. The filtrate was evaporated under reduced pressure to give the title compound (9.6 g, 35 mmol) as a white foam.

GC/MS: M^+ $C_{17}H_{22}NO_2$ 273

Intermediate 3

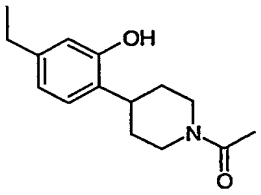
1-[4-(4-Ethyl-2-hydroxy-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-ethanone



The same method was employed as in the preparation of intermediate 1 but starting from 3-ethyl-phenol gave the title compound as a pink solid in a quantitative yield.
GC/MS: M^+ $C_{15}H_{19}NO_2$ 245

Intermediate 4

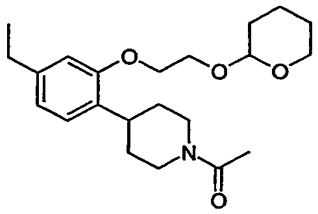
1-[4-(4-Ethyl-2-hydroxy-phenyl)-piperidin-1-yl]-ethanone



The same method was employed as in the preparation of intermediate 2 but starting from intermediate 3 gave the title compound as a solid in a 89% yield.
GC/MS: M^+ $C_{15}H_{21}NO_2$ 247

Intermediate 5

1-(4-{4-Ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidin-1-yl)-ethanone

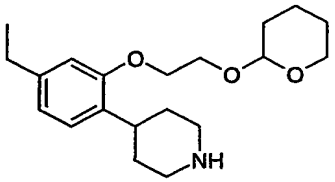


To a solution of intermediate 4 (5 g, 20 mmol) in acetone (200 mL) was added K_2CO_3 (5.52 g, 2 eq.) and the 2-(2-bromo-ethoxy)-tetrahydro-pyran (4.58 mL, 1.5 eq.). The mixture was stirred to reflux for 48 hours and the solvent evaporated. The residue was diluted in DCM and washed with water. The organic layer was dried over Na_2SO_4 and filtered to give the title compound (11.0 g, 27 mmol) as yellow oil in a quantitative yield after chromatography using DCM/MeOH (98/02) as eluent .

GC/MS: M^+ $C_{22}H_{33}NO_4$ 290 (M-Tetrahydropyran)

Intermediate 6

4-{4-Ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidine

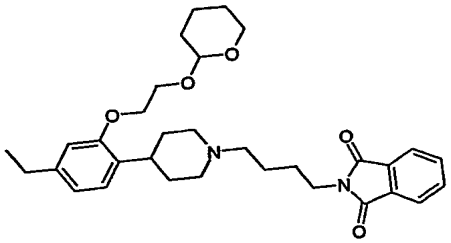


To a solution of intermediate 5 (1.0 eq) in EtOH was added a $NaOH/H_2O$ (1/1) solution and the mixture was stirred to reflux for 24 hours. The solvent was evaporated, water added and the residue extracted with DCM. The organic layer was dried over Na_2SO_4 and the solvent evaporated to give the title compound as brown oil in a 73.4% .

GC/MS: M^+ $C_{20}H_{31}NO_3$ 333

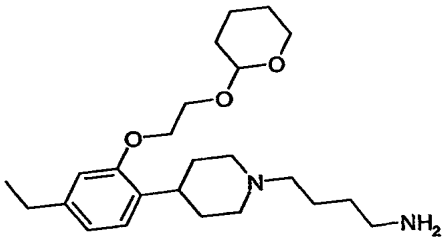
Intermediate 7

2-[4-(4-{4-Ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidin-1-yl)-butyl]-isoindole-1,3-dione



To a solution of intermediate 6 (1.0 eq) in acetone was added K_2CO_3 (2.0 eq.) and 4-bromobutyl-phthalimide (1.0 eq.). The mixture was stirred to reflux for 6 hours and filtered. The filtrate was evaporated and the residue was purified by flash chromatography using DCM/MeOH (95/05) as eluent to give the title compound as a brown oil in a quantitative yield.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.8 (m, 2H), 7.6 (m, 2H), 7 (d, 1H), 6.6 (d, 1H), 6.5 (s, 1H), 5.2 (s, 2H), 4.8 (m, 1H), 4.1-1.1 (m, 32H)

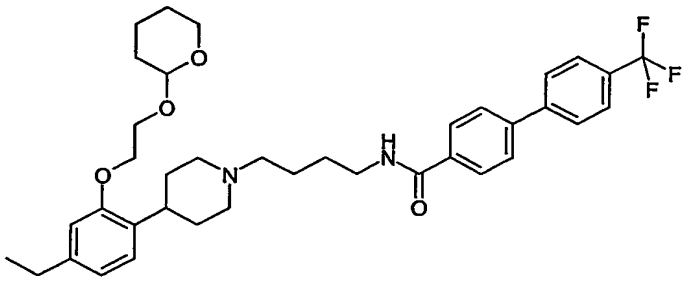
Intermediate 8
4-(4-{4-Ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidin-1-yl)-butylamine



A solution of intermediate 7 (1.0 eq) in MeOH was treated with hydrazine monohydrate (2.0 eq.). The resulting mixture was stirred to reflux for 16 hours. After cooling to rt, and evaporation under reduced pressure the residue was taken up in water and a 1N HCl solution was added until pH=4. Filtration gave yellow solution that was treated with a concentrated NaOH solution. Extraction with DCM ,drying over Na_2SO_4 and filtration gave the title compound as a brown oil in a 78% yield.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.1 (d, 1H), 6.7 (d, 1H), 6.6 (s, 1H), 5.2 (s, 2H), 4.8 (m, 1H), 4.1-1.1 (m, 34H)

Intermediate 9

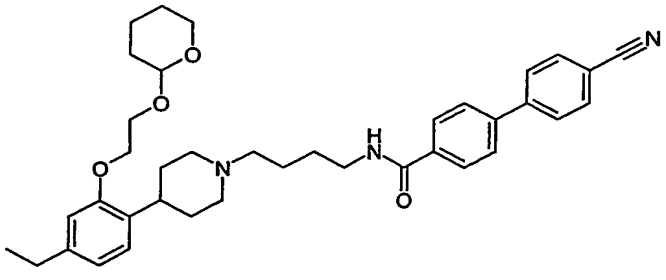
4'-Trifluoromethyl-biphenyl-4-carboxylic acid [4-(4-{4-ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidin-1-yl)-butyl]-amide



A solution of intermediate 8 (1.0eq) in DMF was treated with 4'-trifluoromethyl-biphenyl-4-carboxylic acid (1.0 eq.), EDCI (1.5 eq.), HOBT (1.5 eq.) and TEA (1.5 eq.). The resulting mixture was stirred for 24 hours at rt, and the solvent evaporated. The residue was diluted with DCM and washed with water and with a 1N NaOH solution. The organic layer was dried over Na_2SO_4 and evaporated off. After purification by flash chromatography using DCM/MeOH (95/5) as eluent, the title compound was obtained as white crystals in a 27% yield.
LC/MS: M+H $C_{38}H_{48}F_3N_2O_4$ 653

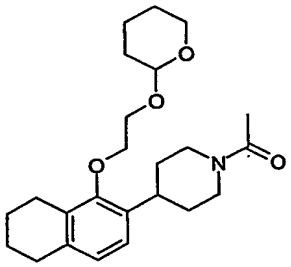
Intermediate 10

4'-Cyano-biphenyl-4-carboxylic acid [4-(4-{4-ethyl-2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-piperidin-1-yl)-butyl]-amide



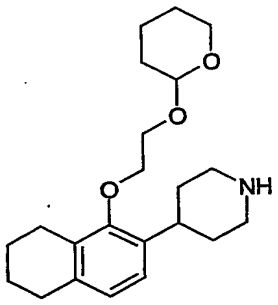
The same method was employed as in the preparation of intermediate 9 but starting from the available 4'-cyano-biphenyl-4-carboxylic acid gave the title compound as a yellow oil in a 20% yield.
LC/MS: M+H $C_{38}H_{48}N_3O_4$ 610

Intermediate 11
1-(4-{1-[2-(Tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-ethanone



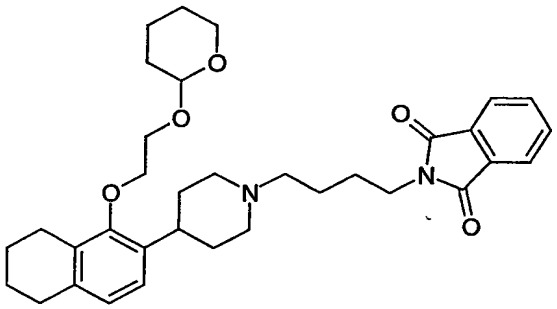
The same method was employed as in the preparation of intermediate 5 but starting from intermediate 2 gave the title compound as a yellow oil in a 95% yield.
LC/MS: M+H $C_{24}H_{36}NO_4$ 402

Intermediate 12
4-{1-[2-(Tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidine



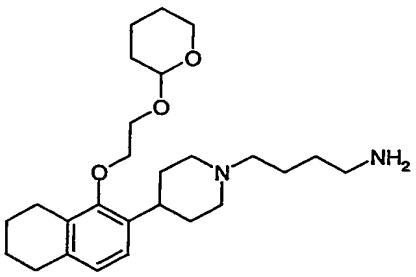
The same method was employed as in the preparation of intermediate 6 but starting from intermediate 11 gave the title compound as yellow oil in a quantitative yield.
LC/MS: M+H $C_{22}H_{34}NO_3$ 360

Intermediate 13
2-[4-(4-{1-[2-(Tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-butyl]-isoindole-1,3-dione



The same method was employed as in the preparation of intermediate 7 but starting from intermediate 12 gave the title compound as a yellow oil in a 93% yield.
LC/MS: M+H $C_{34}H_{45}N_2O_5$ 561

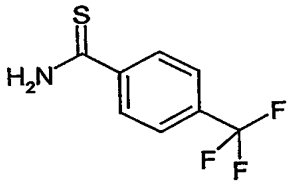
Intermediate 14
4-(4-{1-[2-(Tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-butylamine



The same method was employed as in the preparation of intermediate 8 but starting from intermediate 13 gave the title compound as a yellow oil (contained 30% of formed pyridazine dione).

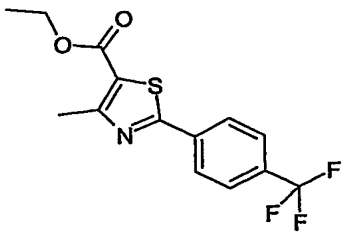
LC/MS: M+H $C_{26}H_{43}N_2O_3$ 431

Intermediate 15
4-Trifluoromethyl-thiobenzamide



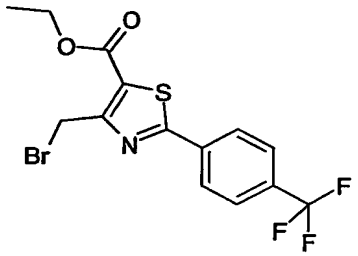
A solution of α,α,α-trifluoro-p-tolunitrile (603.5 g, 3.53 mol) in dry DMF (2 L) under N_2 was heated at 70°C and the thioacetamide (505 g, 1.9 eq.) was added. The reaction mixture was treated with HCl gas for 15 minutes and stirred at 95°C for 6 hours. This treatment was repeated 3 times and the mixture stirred at rt for 24 hours. After cooling at 0°C, water was added and the residue extracted with diethyl ether (4 L). The organic layer was washed with water (3 L), dried over Na_2SO_4 and the solvent evaporated. The brownish powder was washed with pentane (3 L) to give the title compound (530.3g, 2.59 mol) as a brown solid in a 73% yield.
GC/MS: M^+ $C_8H_6F_3NS$ 205

Intermediate 16
4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester



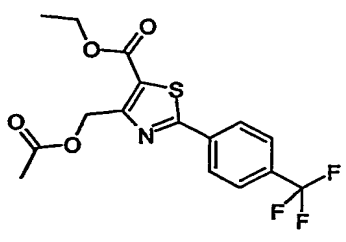
To a solution of intermediate 15 (530.3 g, 2.59 mol) in EtOH (2.6 L) was added 2-chloro-3-oxo-butyric acid ethyl ester (465 mL, 1.3 eq.). The mixture was stirred at rt for 7 hours and at 70°C for 14 hours. After cooling at 0°C, the precipitate was filtered off and washed with cold EtOH (500 mL) to give the title compound (573.0 g, 1.89 mol) as a beige powder in a 73% yield.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.9 (d, 2H), 7.6 (d, 2H), 4.3 (q, 2H), 2.65 (s, 3H), 1.25 (t, 3H).

Intermediate 17
4-Bromomethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester



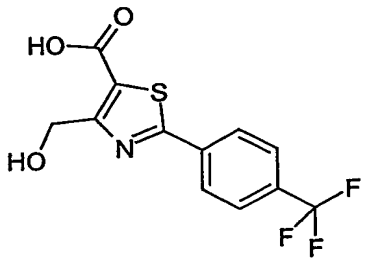
To a solution of intermediate 16 (15.75 g, 50.0 mmol) in CCl_4 was added slowly N-bromosuccinimide (8.9 g, 1.1 eq.) and AIBN (1 g, 10%mol). The mixture was stirred at 80°C for 3 hours, filtered off and the filtrate evaporated. After purification by flash chromatography, using DCM/Cyclohexane (60/40) as eluent, the title compound (4.9 g, 12.5 mmol) was obtained as white solid in a 25% yield.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.2 (d, 2H), 7.8 (d, 2H), 5.1 (s, 2H), 4.5 (q, 2H), 1.3 (t, 3H)

Intermediate 18
4-Acetoxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid ethyl ester



To a solution of intermediate 17 (4.9 g, 12.5 mmol) in AcOH (15 mL) was added sodium acetate (2.0 g, 2eq.). The mixture was stirred to reflux for 14 hours, and after cooling at rt, the mixture was diluted with water (150 mL) and extracted with diethyl ether (250 mL). The organic layer was washed with a 1 N NaOH solution, dried over Na_2SO_4 and the solvent evaporated. The title compound (3.24 g, 8.7 mmol) was obtained as white crystals in a 72% yield.
MP: 82°C

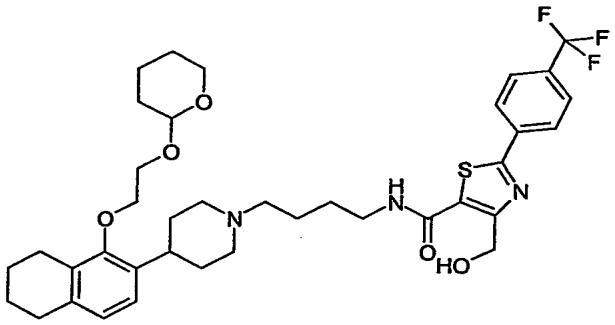
Intermediate 19
4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid



To a solution of intermediate 18 (3.24 g, 8.7 mmol) in EtOH/H_2O (40 mL/20mL) was added the NaOH (1.4 g, 4 eq.) and the mixture was stirred to reflux for 2 hours. After partial evaporation, water (100 mL) was added and treated with a concentrated HCl solution to obtain pH = 1. The precipitate was filtered off, washed with water and dried to give the title compound (2.38 g, 7.8 mmol) as white solid in a 90% yield.
MP: 250-252 °C

Intermediate 20

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid [4-(4-{1-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-butyl]-amide

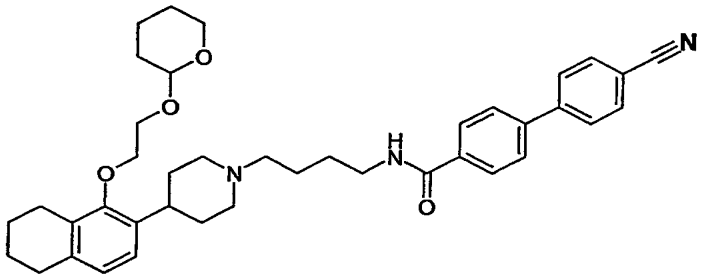


The same method was employed as in the preparation of the intermediate 9 but starting from intermediate 14 and intermediate 19 gave the title compound as a beige powder in a 28% yield.

MP: 146-148°C

Intermediate 21

4'-Cyano-biphenyl-4-carboxylic acid [4-(4-{1-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-5,6,7,8-tetrahydro-naphthalen-2-yl}-piperidin-1-yl)-butyl]-amide

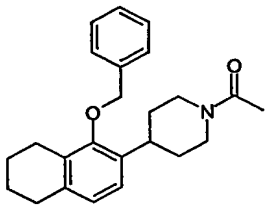


The same method was employed as in the preparation of intermediate 9 but starting from intermediate 14 and 4'-cyano-biphenyl-4-carboxylic acid gave the title compound as white oil in a 62% yield.

LC/MS: M+H $C_{40}H_{49}N_3O_4$ 636

Intermediate 22

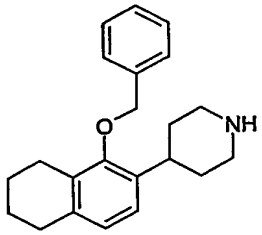
1-[4-(1-Benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-ethanone



A solution of intermediate 2 (11 g, 40 mmol), K_2CO_3 (19.0 g, 1.5 eq.) in methyl ethyl ketone (150 mL) was stirred at 80°C for 10 minutes. Benzyl bromide (7.7 g, 1.1 eq.) was added and the mixture was stirred to reflux for 2.5 hours. After filtration, the filtrate was evaporated and the residue washed with water, extracted with ether and evaporated off. The solid was washed with iPr_2O to give the title compound (9.5 g, 26.2 mmol) as beige crystals in a 66% yield.
MP: 108-110 °C

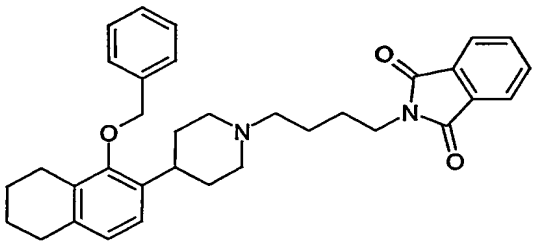
Intermediate 23

4-(1-Benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidine



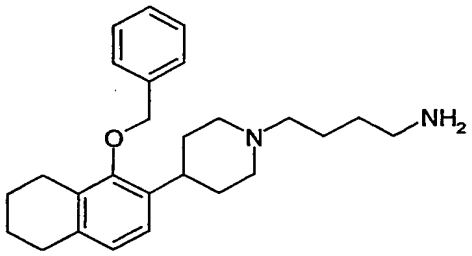
The same method was employed as in the preparation of intermediate 6 but starting from intermediate 22 gave the title compound as oil in a 98% yield directly used in the next step without purification.
LC/MS: M+H $C_{22}H_{28}NO$ 322

Intermediate 24
2-{4-[4-(1-Benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione



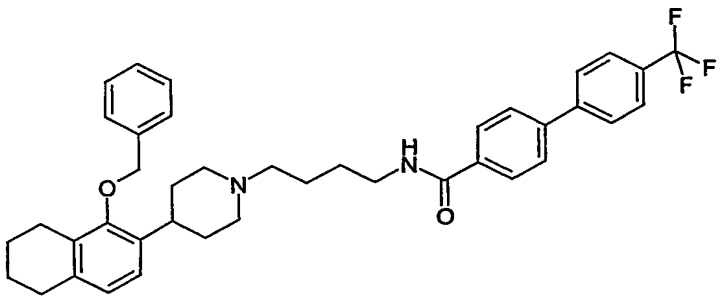
The same method was employed as in the preparation of intermediate 7 but starting from intermediate 23 gave the title compound as an oil in a quantitative yield directly used in the next step without purification.
LC/MS: M+H $C_{34}H_{39}N_2O_3$ 523

Intermediate 25
4-[4-(1-Benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butylamine



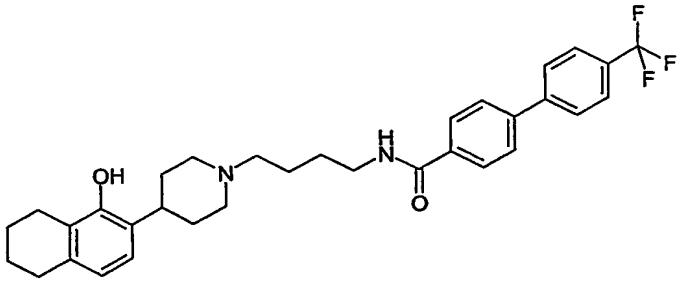
The same method was employed as in the preparation of intermediate 8 but starting from intermediate 24 gave the title compound as an oil in a 59% yield directly used in the next step without purification.
LC/MS: M+H $C_{26}H_{37}N_2O$ 393

Intermediate 26
4'-Trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1-benzyloxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide



The same method was employed as in the preparation of intermediate 9 but starting from intermediate 25 and 4'-trifluoromethyl-biphenyl-4-carboxylic acid gave the title compound as white crystals in 45% yield after recrystallisation in CH_3CN.
MP: 169-170°C

Intermediate 27
4'-Trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1-hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide

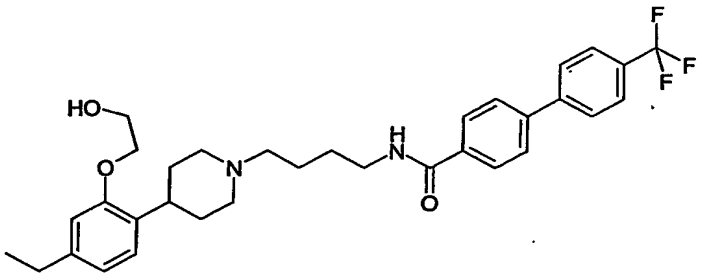


To a mixture of intermediate 26 (4.0 g, 6.2 mmol) in EtOH (150 mL) was added Pd/C,10% (0.6 g) and the reaction stirred under an atmospheric pressure of hydrogen at 60°C for 2 hours. The mixture was filtered through a bed of celite.

The filtrate was evaporated under reduced pressure to give the title compound (3 g, 5.4 mmol) as a white crystals after crystallisation from EtOH.
MP: 220-222°C

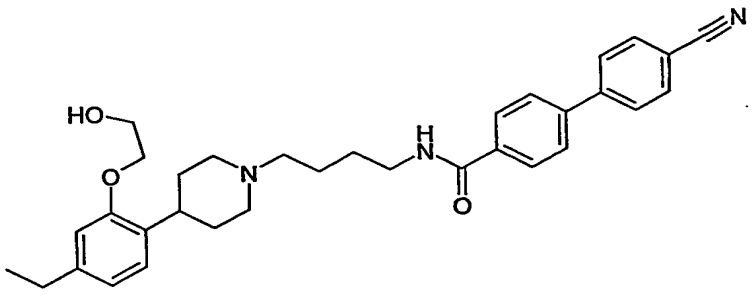
EXAMPLES

Example 1 :
4'-Trifluoromethyl-biphenyl-4-carboxylic acid (5-{4-[4-ethyl-2-(2-hydroxy-ethoxy)-phenyl]-piperidin-1-yl}-butyl)-amide hydrochloride



To a solution of intermediate 9 (0.28 g, 0.43 mmol) in MeOH/DCM 50/50 (20 mL) was added a 1N HCl solution (0.9 ml, 2 eq.) and the resulting mixture stirred at rt for 24 hours. The solvent was evaporated off and the residue treated with DCM/iPr_2O to give the title compound (0.080 g, 0.13 mmol) as white crystals in 31% yield.
^1H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, 2H), 7.8 (d, 6H), 7.15 (d, 1H), 6.8 (m, 2H), 4.2 (m, 4H), 3.8 (m, 4H), 3.2 (m, 2H), 3-1.8 (m, 15H), 1.3 (t, 3H).
LC/Tof : ES^+ 569.2946 7.8 ppm

Example 2 :
4'-Cyano-biphenyl-4-carboxylic acid (5-{4-[4-ethyl-2-(2-hydroxy-ethoxy)-phenyl]-piperidin-1-yl}-butyl)-amide hydrochloride



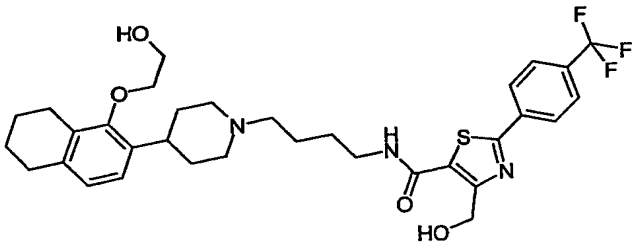
The same method was employed as in the preparation of example 1 but starting from intermediate 10 gave the title compound as white crystals in a 8% yield after recrystallisation in iPr_2O.

LC/Tof : ES^+ 526.3093 4.6 ppm

^1H NMR ($CDCl_3$, 300 MHz) δ 8.1 (d, 2H), 7.7 (d, 6H), 6.95 (d, 1H), 6.7 (m, 2H), 4.2 (m, 4H), 4.0 (m, 4H), 3.4 (m, 2H), 3.1-1.6 (m, 15H), 1.2 (t, 3H).

Example 3 :

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid (4-{4-[1-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide



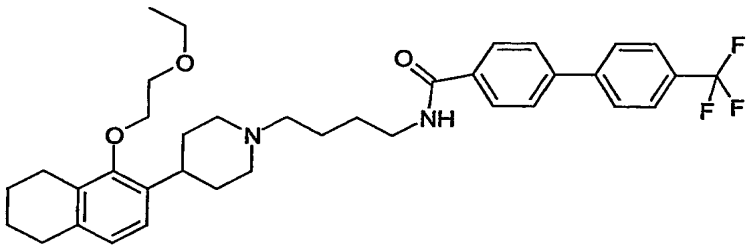
The same method was employed as in the preparation of example 1 but starting from intermediate 20 gave the title compound as beige crystals in a 39% yield after recrystallisation in CH_3CN.

MP: 157-159°C

LC/MS : M+H $C_{33}H_{41}F_3N_3O_4S$ 632

Example 4 :

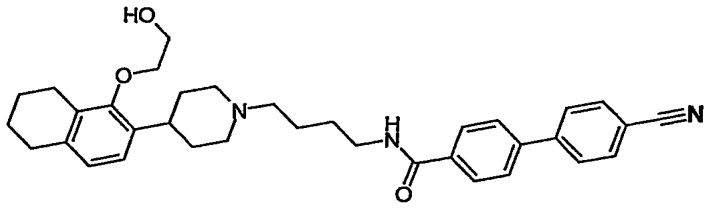
4'-Trifluoromethyl-biphenyl-4-carboxylic acid (4-{4-[1-(2-ethoxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide



To a solution of TMAD (2.0 eq.) in dry THF under argon was added tributylphosphine (2.2 eq.). The mixture was stirred at rt for 10 minutes. Then intermediate 27 (1.0 eq) and 2-ethoxy-ethanol (1.2 eq.) were added and the mixture was stirred at rt for 48 hours. The water was added and the reaction mixture evaporated off . The residue was taken in water and the precipitate was filtered off. After recrystallisation in CH_3CN, the title compound was obtained as white crystals in a 81% yield.
MP: 190°C
LC/Tof: ES^+ 623.3485 3.8 ppm

Example 5 :

4'-Cyano-biphenyl-4-carboxylic acid (4-{4-[1-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide hydrochloride



The same method was employed as in the preparation of example 1 but starting from intermediate 21 gave the title compound as white crystals in a 77% yield after recrystallisation in $iPrO_2$.

MP: 174°C
LC/tof: ES^+ 552.3176 9 ppm

Biological Assays

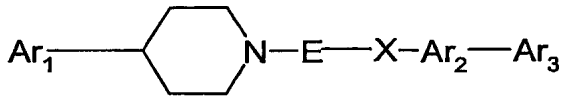
In Vitro Assay :
$HepG_2$ cells, stably transfected with a construct comprising the LDL-r promoter and the luciferase reporter gene, were seeded at 50.000 cells/well in 96 well plates. After 1 day, cells were incubated with compounds for 24 hours in RPMI medium containing 2% of lipoprotein-deficient serum. Compounds were tested from 10^{-6}M to 10^{-9}M.Cell lysates were prepared and the luciferase activity was measured by the luciferase assay system (Promega). Induction of luciferase activity was calculated taking untreated cells as control and ED_{50} of each compounds was determined compared to the ED_{50} of an internal standard.

In Vivo Assay :
Compounds were prepared for oral administration by milling with 0.5% hydroxypropylmethylcellulose and 5% Tween 80. Hamsters were fed for 2 weeks with a diet containing 0.2% of cholesterol and 10% of coconut oil. Then compounds were administered once a day for 3 days, from 20 to 0.2mg/kg. Plasma lipid levels including total cholesterol, VLDL/LDL cholesterol, VLDL/LDL triglycerides and HDL-cholesterol were determined after ultracentrifugation (density 1.063g/ml to separate VLDL/LDL fraction and HDL fraction) using the Biomerieux enzymatic kit. Reductions in VLDL/LDL cholesterol and TG plasmatic levels were calculated taking solvent treated animals as control and ED_{50} of each compound was determined.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A compound of formula (I)



(I)

wherein

Ar_1 represents

(iii) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl , or

(iv) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that at least one ring is aromatic,

where Ar_1 bears at least one group independently represented by R^1 and 0-3 groups independently represented by R^3;

R^1 is $O(CH_2)_nOR^2$;

R^2 is H or $(CH_2)_mCH_3$;

n is 1-4;

m is 0-4;

R^3 is selected from halogen, -O-(C_{0-4} alkylene)-R^4 or –(C_{0-4}alkylene)-R^4, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms ;

R^4 represents

(v) hydrogen, C_{1-4} perfluoroalkyl, C_{1-4}perfluoroalkoxy,

(vi) phenyl, phenyl fused by a C_{3-8}cycloalkyl , naphthyl or a 5- or 6-membered heteroaromatic group, optionally substituted by one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino,

(vii) C_{3-8}cycloalkyl or a monocyclic heterocyclyl radical containing a total of 3-7 ring atoms, wherein said radical contains a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein said radical may be independently saturated, partially unsaturated, or aromatic, and where the C_{3-8}cycloalkyl or a monocyclic heterocyclyl may bear one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino, or

(viii) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino;

Ar_2 represents phenyl or a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, where each group is optionally substituted by one or two groups independently selected from the group consisting of: C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, C_{1-6} acyl, C_{1-6} acyloxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino groups;

Ar_3 represents

(iii) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl,

(iv) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

where Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkoxy, C_{1-4} acylamino or an electron withdrawing group selected

from the list consisting of: nitrile, nitro, C_{1-4}, C_{1-4} perfluoroalkyl, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylaminosulfonyl and di-C_{1-4} alkylaminosulfonyl, C_{1-4} alkylsulfonyl and C_{1-4}alkylsulfoxy;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

or a physiologically acceptable prodrug, salt or solvate thereof.

2. A compound selected from

4'-Trifluoromethyl-biphenyl-4-carboxylic acid (5-{4-[4-ethyl-2-(2-hydroxy-ethoxy)-phenyl]-piperidin-1-yl}-pentyl)-amide hydrochloride;

4'-Cyano-biphenyl-4-carboxylic acid (5-{4-[4-ethyl-2-(2-hydroxy-ethoxy)-phenyl]-piperidin-1-yl}-pentyl)-amide hydrochloride;

4-Hydroxymethyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid (4-{4-[3-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide;

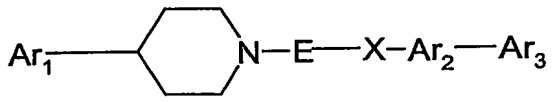
4'-Trifluoromethyl-biphenyl-4-carboxylic acid (4-{4-[1-(2-ethoxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide;

4'-Cyano-biphenyl-4-carboxylic acid (4-{4-[1-(2-hydroxy-ethoxy)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}-butyl)-amide hydrochloride;

or a physiologically acceptable salt, solvate or derivative thereof.

ABSTRACT

The invention relates to a compound of formula (I)



(I)

wherein

Ar_1 represents

(v) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl , or

(vi) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that at least one ring is aromatic,

where Ar_1 bears at least one group independently represented by R^1 and 0-3 groups independently represented by R^3;

R^1 is $O(CH_2)_nOR^2$;

R^2 is H or $(CH_2)_mCH_3$;

n is 1-4;

m is 0-4;

R^3 is selected from halogen, -O-(C_{0-4} alkylene)-R^4 or –(C_{0-4}alkylene)-R^4, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms ;

R^4 represents

(ix) hydrogen, C_{1-4} perfluoroalkyl, C_{1-4}perfluoroalkoxy,

(x) phenyl, phenyl fused by a C_{3-8}cycloalkyl , naphthyl or a 5- or 6-membered heteroaromatic group, optionally substituted by one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino,

(xi) C_{3-8}cycloalkyl or a monocyclic heterocyclyl radical containing a total of 3-7 ring atoms, wherein said radical contains a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein said radical may be independently saturated, partially unsaturated, or aromatic, and where the C_{3-8}cycloalkyl or a monocyclic heterocyclyl may bear one or two groups independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino, or

(xii) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino;

Ar_2 represents phenyl or a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, where each group is optionally substituted by one or two groups independently selected from the group consisting of: C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, C_{1-6} acyl, C_{1-6} acyloxy, amino, C_{1-4} alkylamino and di-C_{1-4} alkylamino groups;

Ar_3 represents

(v) phenyl, naphthyl, or phenyl fused by a C_{3-8}cycloalkyl,

(vi) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

where Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkoxy, C_{1-4} acylamino or an electron withdrawing group selected

from the list consisting of: nitrile, nitro, C_{1-4}, C_{1-4} perfluoroalkyl, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylaminosulfonyl and di-C_{1-4} alkylaminosulfonyl, C_{1-4} alkylsulfonyl and C_{1-4}alkylsulfoxy;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

or a physiologically acceptable prodrug, salt or solvate thereof.